Paracetamol, alcohol and the liver

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It is claimed that chronic alcoholics are at increased risk of paracetamol (acetaminophen) hepatotoxicity not only following overdosage but also with its therapeutic use. Increased susceptibility is supposed to be due to induction of liver microsomal enzymes by ethanol with increased formation of the toxic metabolite of paracetamol. However, the clinical evidence in support of these claims is anecdotal and the same liver damage after overdosage occurs in patients who are not chronic alcoholics. Many alcoholic patients reported to have liver damage after taking paracetamol with 'therapeutic intent' had clearly taken substantial overdoses. No proper clinical studies have been carried out to investigate the alleged paracetamol–alcohol interaction and acute liver damage has never been produced by therapeutic doses of paracetamol given as a challenge to a chronic alcoholic.

The paracetamol–alcohol interaction is complex; acute and chronic ethanol have opposite effects. In animals, chronic ethanol causes induction of hepatic microsomal enzymes and increases paracetamol hepatotoxicity as expected (ethanol primarily induces CYP2E1 and this isoform is important in the oxidative metabolism of paracetamol). However, in man, chronic alcohol ingestion causes only modest (about twofold) and short-lived induction of CYP2E1, and there is no corresponding increase (as claimed) in the toxic metabolic activation of paracetamol. The paracetamol–ethanol interaction is not specific for any one isoform of cytochrome P450, and it seems that isoenzymes other than CYP2E1 are primarily responsible for the oxidative metabolism of paracetamol in man. Acute ethanol inhibits the microsomal oxidation of paracetamol both in animals and man. This protects against liver damage in animals and there is evidence that it also does so in man. The protective effect disappears when ethanol is eliminated and the relative timing of ethanol and paracetamol intake is critical.

In many of the reports where it is alleged that paracetamol hepatotoxicity was enhanced in chronic alcoholics, the reverse should have been the case because alcohol was actually taken at the same time as the paracetamol. Chronic alcoholics are likely to be most vulnerable to the toxic effects of paracetamol during the first few days of withdrawal but maximum therapeutic doses given at this time have no adverse effect on liver function tests. Although the possibility remains that chronic consumption of alcohol does increase the risk of paracetamol hepatotoxicity in man (perhaps by impairing glutathione synthesis), there is insufficient evidence to support the alleged major toxic interaction. It is astonishing that clinicians and others have unquestioningly accepted this supposed interaction in man for so long with such scant regard for scientific objectivity.

Keywords: CYP2E1, cytochrome P450, ethanol, hepatotoxicity, interaction, isoenzymes, overdose, paracetamol, therapeutic misadventure, therapeutic use

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Received 16 April 1999, accepted 16 December 1999.

Introduction

There have been many reports claiming that the hepatotoxicity of paracetamol (acetaminophen) is increased in chronic alcoholics, and that such individuals not only carry an increased risk of severe and fatal liver damage after acute overdosage [1–20], but that similar serious liver damage may also occur with 'therapeutic' use [5, 9, 10, 17, 18, 21–64]. In the original studies of the mechanisms of toxicity, paracetamol was found to cause liver damage through conversion by hepatic cytochrome P450 enzymes to a minor but toxic intermediate metabolite [65–68] and this was subsequently identified as *N*-acetyl-*p*-benzoquinoneimine [69, 70]. In accordance with this mechanism, the susceptibility to paracetamol-induced liver damage in animals was increased when these enzymes were stimulated by prior administration of inducing agents such as phenobarbitone and 3-methylcholanthrene, and decreased by inhibitors such as piperonyl butoxide and 4-methylpyrazole [65, 66, 71]. Chronic administration of ethanol also causes microsomal enzyme induction in animals and as expected, this increased the metabolic activation and the hepatotoxicity of paracetamol [26, 72–89]. In the circumstances, it was natural to suspect that there might be similar potentiation of paracetamol hepatotoxicity following overdosage in chronic alcoholics and indeed, this had been suggested in an early study in which the outcome of severe paracetamol poisoning in potentially induced patients appeared to be worse than in similar noninduced patients [1]. Subsequently, many anecdotal reports appeared describing severe and sometimes fatal liver damage in chronic alcoholics taking paracetamol in overdosage [2–20], as well as after its use for therapeutic purposes [5, 9, 10, 17, 18, 21–64].

The collective weight of these uncontrolled case reports has been taken uncritically as 'proof' that the hepatotoxicity of paracetamol is increased in chronic alcoholics and it is universally assumed that as in animals, the mechanism is increased production of the toxic metabolite caused by induction of hepatic drug metabolizing enzymes. These beliefs were strengthened further by the demonstration in animals that the primary isoform of cytochrome P450 which is induced by ethanol (CYP2E1) is also involved in the metabolic activation of paracetamol [90–102]. Potentiation of paracetamol hepatotoxicity by chronic consumption of ethanol in man is now accepted as established truth and it has been referred to as a 'classic syndrome of medicine' [60]. As this review will show, however, there is insufficient evidence to justify the claims made for such an interaction in man.

Clinical studies

Paracetamol overdose

However convincing the numerous reports of liver damage following paracetamol overdosage in chronic alcoholics may be [2–20], they are purely anecdotal and the inescapable fact remains that exactly the same severe and fatal liver damage occurs after overdosage in patients who are not chronic alcoholics. The doses claimed to have been taken by the chronic alcoholics ranged from less than 10 g [6, 17, 18, 103] to more than 30 g [5, 10, 15, 18, 20, 104, 105]. Apart from the presence of underlying chronic liver disease in some patients, there is no difference in the clinical course of paracetamol poisoning in alcoholics. However, alcoholics may appear to be more susceptible to the hepatotoxicity of paracetamol because they often present late. Patients who present late are more severely poisoned and have a much worse prognosis than those who come to hospital early, regardless of alcohol intake [106–109]. In addition, the apparent association of severe liver damage and excessive alcohol intake largely reflects a population which is likely to take overdoses [108]. These are important sources of bias that exaggerate the belief that chronic alcoholics suffer more severe liver damage following an overdose of paracetamol.

There have been no proper prospective controlled studies in which the outcome of paracetamol poisoning has been compared in chronic alcoholics and similarly poisoned nonalcoholic patients. In the original study in which it was suggested that enzyme-induced patients are at greater risk of severe liver damage [1], only three of the eight potentially induced patients were chronic alcoholics and it is impossible to draw any conclusion with such small numbers. In a study of selected patients with paracetamol poisoning who had been referred to a specialist liver unit, the prognosis was said to be worse in patients who consumed more than the maximum recommended amount of alcohol compared with that in those who drank less [110]. However, alcohol intake was determined retrospectively from case notes, and this information was missing in an unstated number of patients. In addition, the patients with excessive alcohol intake had taken larger doses of paracetamol. In other reports from the same unit, it was not possible to show that the outcome was worse in patients with previous excessive intake of alcohol [106, 108]. In other large-scale studies of paracetamol poisoning, the severity of liver damage and the prognosis were not adversely affected by alcoholism [111–114]. A more recent report indicated that liver damage following paracetamol overdose, as shown by aminotransferase activity, was greater in at risk patients with chronic use of ethanol than in those without. Chronic ethanol did not increase liver toxicity among low risk cases [115]. Other investigators

have suggested that potentiation of paracetamol hepatotoxicity in such patients was due not so much to the effects of the alcohol as to poor diet and fasting [17]. Fasting increases paracetamol hepatotoxicity in rats by decreasing glucuronide and sulphate conjugation so that the proportion converted to the toxic metabolite is significantly enhanced [116]. A similar mechanism has never been demonstrated in man.

Overall, there is no consistent clinical evidence that chronic alcoholics are at significantly increased risk of liver damage, or that they have a uniformly worse prognosis following an overdose of paracetamol. If this were the case, many chronic alcoholics would develop severe liver damage at normally nontoxic plasma paracetamol concentrations, below the standard treatment line. In fact, there have only been isolated reports of such cases [13, 16, 20, 117].

Use of paracetamol with 'therapeutic intent' – 'therapeutic misadventure'

Many of the patients involved in the numerous anecdotal case reports of severe and sometimes fatal liver damage following the apparently innocent use of paracetamol with 'therapeutic intent' have been chronic alcoholics [5, 9, 10, 17, 18, 21–64]. At first sight, it seems that most of these unfortunate patients had taken normal, or little more than normal doses of paracetamol for short periods because of symptoms such as pain, and that there were no warning signs before the onset of liver damage. However, the clinical picture on presentation was invariably typical of an acute overdose taken 3 or 4 days previously with the maximum elevation of aminotransferases usually occurring on the day of admission followed by a rapid return to normal. Such a pattern would not be seen if, as often claimed, the drug had been taken regularly over a period of several days up to the time of admission. As might be expected following acute overdosage, some patients developed renal failure and some died in hepatic failure [4, 5, 8, 22, 23, 26, 33, 34, 37, 40, 48]. In many of the chronic alcoholic patients it is clear from the history [10, 17, 18, 21, 27, 29, 33, 39, 49, 60] and from plasma paracetamol measurements (when available) [24, 32, 37, 40], that major overdoses had been taken. It seems that in their haste to draw attention to the perceived dangers of paracetamol, many authors have failed to distinguish between a 'therapeutic dose' and 'therapeutic intent', and a maximum single dose (1 g) and a maximum divided daily dose (4 g). Similarly, gross overdosage such as ingestion of 10–25 g daily can hardly be described as 'therapeutic misadventure' [17, 18, 21, 26, 27, 29, 33, 39, 49, 60]. The volume of these reports has been increased by reporting the same patients more than once [9, 10, 25, 26, 39, 60, 118], and by endlessly repeated reviews of published cases [39, 41, 47, 58, 60, 62, 119, 120]. It should also be noted that the two largest and most recent reviews were supported financially by companies producing analgesics which compete with paracetamol [58, 60]. The presumed toxic interaction between paracetamol and alcohol has also been the subject of scores of uncritical and often poorly informed comments and editorials.

It is very difficult to accept that single and repeated daily doses of as little as 1–3 g paracetamol could cause severe and fatal liver damage in alcoholics as claimed [9, 24, 25, 30, 32, 37, 39, 40, 42, 46, 51, 52, 55, 60]. In one report, 67 cases of 'therapeutic misadventure' in chronic alcoholics were solicited by word of mouth or letter from colleagues and 27 allegedly took less than 4 g paracetamol daily [60]. The drug history must always be suspect in chronic alcoholics. Some 5–8% of a therapeutic dose of paracetamol is normally converted to the toxic metabolite and according to the hepatic content of glutathione, the theoretical single hepatotoxic dose in an adult is normally about 15 g [121]. This agrees well with the threshold dose of 150–250 mg kg^{-1} observed in poisoned patients [122]. Even if the whole of a therapeutic dose were converted to the toxic metabolite in the patients mentioned above, it could hardly be sufficient to produce any degree of liver damage let alone fatal hepatic failure.

In the absence of control data these anecdotal case reports in themselves cannot 'prove' that therapeutic doses of paracetamol cause liver injury in chronic alcoholics. The fact that there are similar (but sometimes equally suspect) reports of patients who were not chronic alcoholics [7, 18, 40, 41, 58, 103, 123–127] is conveniently overlooked. Indeed, if paracetamol in normal doses is as dangerous in chronic alcoholics as it is claimed, liver damage should be commonplace considering the enormous scale on which the drug is used and the prevalence of alcoholism. In one survey, nearly a third of chronic alcoholics admitted to taking paracetamol regularly and reports of abuse were frequent with almost 5% fitting the patterns of drinking and use that are theoretically associated with hepatotoxicity [120]. Where are all these patients? Some alcoholics can be extraordinarily resistant to paracetamol and one such individual apparently took 15–25 g paracetamol daily for 5 years without evidence of liver toxicity [128]. Finally, and most importantly, *there has never been a single documented instance of any degree of acute liver damage produced by therapeutic doses of paracetamol given as a challenge in any chronic alcoholic under properly controlled conditions*. If paracetamol is as dangerous in the chronic alcoholic as claimed by so many investigators, why has no such example been published? It is accepted that proper challenge studies in chronic alcoholics are not easy but there should be no great risk with the supervised administration of appropriately graded doses of paracetamol.

Acute *vs* chronic ethanol

The position is complicated enormously because acute and chronic consumption of ethanol can have opposite effects on paracetamol hepatotoxicity. When a single dose of ethanol is given at or about the same time as paracetamol, it protects animals against hepatotoxicity even if they have been sensitized by previous chronic administration of alcohol [71, 78, 81, 85, 129–134] . This protective effect is associated with inhibition of the toxic metabolic activation of paracetamol both *in vivo* [79, 82, 134–136] and *in vitro* [136, 137]. Ethanol protects at concentrations as low as 2 mM [137] but once it has disappeared from the system, paracetamol metabolism reverts to the previous state. With acute ingestion, the timing in relation to the taking of the paracetamol is critical [71, 76, 83, 85, 131, 138] and in certain circumstances the effects of acute and chronic ethanol tend to cancel out [79, 102]. The protective effect of a single dose of ethanol decreases progressively as the time interval between the administration of ethanol and paracetamol increases. In mice, protection is lost after 6 h [85] and toxicity is greatly increased after a delay of 16–18 h, presumably as a result of enzyme induction [83, 138]. The effect of ethanol on the metabolic activation of paracetamol is generally thought to be caused by competitive inhibition. However, it seems to produce less inhibition *in vitro* than *in vivo*, and an alternative mechanism based on the depletion of cytosolic NADPH has been proposed [71, 136].

In contrast, the chronic administration of ethanol increases the hepatotoxicity and lethality of paracetamol in animals provided that sufficient time is allowed for the elimination of the ethanol after the last dose [26, 72, 74–78, 80–83, 85–89, 133, 139–142]. This effect is usually associated with microsomal enzyme induction with enhanced metabolic activation of paracetamol as shown by increased production of its glutathione-derived conjugates [73, 78, 79, 84, 86]. However, there have been some anomalous findings. Thus chronic ethanol did not always cause induction [76, 81, 82, 143], and hamsters treated with chronic ethanol and then withdrawn from it for 24 h were more resistant to the toxicity of paracetamol than control animals not exposed to ethanol [76]. Nevertheless, the potentiation of the hepatotoxicity of paracetamol by chronic ethanol intake in animals forms the mainstay of the belief that there is similar enhancement of toxicity in chronic alcoholics.

In man, acute ethanol has exactly the same inhibitory effect on the oxidative metabolism of paracetamol as it does in animals. Thus alcohol inhibited the toxic metabolic activation of paracetamol by human liver microsomes [71] and it produced a major reduction in the fractional urinary excretion of the cysteine and mercapturic acid conjugates of paracetamol in healthy nonalcoholic volunteers [144–147] as well as in heavy drinkers [148]. A substantial proportion of patients who take overdoses of paracetamol have also taken alcohol at the same time [18, 107, 109, 112, 149] and this appears to protect them against liver damage [111, 150]. The protective action of alcohol taken at the time of an overdose probably adds significantly to the large individual variation in susceptibility to the toxicity of paracetamol.

Chronic excessive use of ethanol undoubtedly causes short-term induction of CYP2E1 in man. CYP2E1 activity was increased by a factor of two in alcoholics who were still drinking but this effect was short-lived and activity was not increased after abstinence for more than 5–10 days [151]. Incubation of primary hepatocyte cultures from three human livers with ethanol for 92 h also induced CYP2E1 activity but the extent of induction varied [152]. However, in another study, chronic alcoholics showed no enhancement of activity unless they had active liver damage [153]. Hydroxylation of chlorzoxazone has been used as a probe for CYP2E1 activity and the metabolic ratio was increased in chronic alcoholics although activity decreased with increasing severity of alcoholic liver disease [154, 155]. The short duration of induction of CYP2E1 by ethanol in man was confirmed in another study in which the metabolic ratio of chlorzoxazone returned to control levels in chronic alcoholics after they had abstained for 8 days [156]. Taken together, these studies indicate only modest, variable and short-lived induction of CYP2E1 by ethanol in man. The induction of CYP2E1 by ethanol in animals is dose-dependent and multiple mechanisms are involved including increased synthesis of mRNA and stabilization of the 2E1 protein [102, 157]. With the latter mechanism there is likely to be binding of ethanol to the active site of the enzyme and this would probably cause simultaneous inhibition and induction [102].

Insufficient attention has been given to the timing of alcohol intake in relation to paracetamol consumption and toxicity in clinical reports. If the same circumstances apply in man as in animals, alcohol could increase or decrease the toxicity of paracetamol, or have no effect, depending on the timing and duration of alcohol consumption. In some reports purporting to show that chronic alcoholics are at increased risk of paracetamol hepatotoxicity, alcohol seems to have been taken acutely at or about the same time as the paracetamol [2, 4, 6, 11, 12, 18, 22, 23, 33, 35, 39, 48, 53, 55, 59, 61, 63]. In these cases, the alcohol should have reduced paracetamol toxicity rather than enhanced it as claimed!

Chronic alcoholics are likely to be at their most vulnerable during the first few days after stopping their regular drinking when the ethanol has been completely eliminated because at this time any induction would be unopposed [102, 157]. It is true that this pattern of events

has been described in some patients who developed paracetamol-induced liver damage shortly after discontinuing their regular intake of alcohol because of illness or injury [6, 11, 13, 21, 34, 37, 39, 44, 54]. It follows that the definitive test to determine whether normal therapeutic doses of paracetamol could cause severe hepatic injury in chronic alcoholics would be to give it during the first few days of alcohol withdrawal. Such a study has indeed been carried out. Sixty withdrawing alcoholic inpatients were given either paracetamol 1 g 4 times daily or placebo for 2 days with biochemical monitoring on days 2 and 4. There were no differences between the groups in respect of hepatic and renal function [158]. In another report, routine screening for 48 h of 373 patients admitted to an alcohol detoxification unit failed to reveal any instance of paracetamol hepatotoxicity [159]. These negative findings make it most unlikely that chronic alcoholics are at significant risk of hepatotoxicity following the normal therapeutic use of paracetamol.

Paracetamol metabolism in chronic alcoholics

If chronic consumption of ethanol does cause induction of microsomal enzymes in man with stimulation of the metabolic activation of paracetamol and enhanced toxicity as claimed, it follows that there should be a substantial increase in the formation of glutathione-derived metabolites and a corresponding increase in the fractional urinary excretion of the cysteine and mercapturic acid conjugates. In one report, the recovery of these metabolites was increased (although remaining well within normal limits) in abstaining alcoholics without liver disease [160] and in another, chronic alcoholics in withdrawal produced more glutathione-derived metabolites of paracetamol than healthy subjects although the increase was minimal and barely of statistical significance [161]. In studies of the time course of induction and inhibition of paracetamol metabolism by ethanol, healthy volunteers were given 6 h infusions of ethanol or dextrose solution on two separate occasions. On the first, they received 500 mg of paracetamol 30 min after the start of the infusion and on the second the same dose was taken 8 h after the end of the infusion. When paracetamol was taken with the ethanol infusion there was a 72% reduction in the formation of the toxic metabolite but when it was taken 8 h after stopping the infusion there was a modest but toxicologically insignificant increase of 24% [147]. Other investigators have failed to demonstrate any increase in the toxic metabolic activation of paracetamol in heavy drinkers [148] or in abstaining chronic alcoholics [162]. In one chronic alcoholic who apparently took 15–25 g paracetamol daily without liver damage, there was no evidence of increased toxic metabolic activation [128]. When chronic alcoholics were studied within 48 h of abstinence from alcohol and again after 15 days, there was no decrease in the 24 h urinary excretion of the mercapturic acid conjugate of paracetamol as would be expected had they been induced [163]. Claims that an increased clearance of paracetamol in abstaining chronic alcoholics is evidence of enhanced hepatotoxicity [164, 165] can be discounted because this would largely reflect changes in the major elimination pathway of glucuronide conjugation, and no conclusions can be drawn concerning any effects on the minor route of toxic metabolic activation. Indeed, all other things being equal, induction of glucuronide conjugation would actually reduce the risk of paracetamol hepatotoxicity. In another study, the plasma paracetamol half-life (based on very limited sampling) was not abnormal in chronic alcoholics and was not related to the different genotypes of CYP2E1 [166].

Taken together, these studies indicate that formation of the toxic metabolite of paracetamol is not increased to a toxicologically significant extent in chronic alcoholics and in this respect, the situation in man differs from that in animals. Nevertheless, it is important to recognize that chronic alcoholics are likely to be at greatest risk during withdrawal when any effect of induction on the metabolic activation of paracetamol would no longer be countered by the inhibitory effects of circulating ethanol. If chronic alcoholics really do have an increased susceptibility to the hepatotoxicity of paracetamol, then it seems that a mechanism other than induction of CYP2E1 must be responsible. In this context glutathione functions as an important defence mechanism against paracetamol hepatotoxicity and it has been suggested that chronic alcoholics could be at increased risk because of a reduced capacity for glutathione synthesis [162, 167].

Isoenzyme specificity

Much has been made of the observation that in animals the major isoform of cytochrome P450 induced by ethanol (CYP2E1) also plays an important role in the toxic metabolic activation of paracetamol [17, 18, 49, 60, 87, 90, 92–98, 100–102, 155, 165, 166, 168] and the finding that the human isoenzyme also converted paracetamol to its potentially toxic metabolite seemed to settle the matter [58, 60, 93, 96, 97, 157, 169]. However, most of these studies were carried out in mice, rats and rabbits and in one study with human CYP2E1, activity was demonstrated at the supratoxic concentration of $1500\,mg\,l^{-1}$ [96]. Subsequent investigation at more clinically realistic concentrations indicated only a minor role for CYP2E1 and that CYP3A4 was probably more important [170]. Many isoforms of cytochrome P450 including 1A1, 1A2, 2A1, 2A6, 2B1, 2C11, 2C12, 2E1, 3A1 and 3A4 contribute to the metabolism of paracetamol [95, 97, 169, 171]. More recent studies indicate important

roles for CYP1A2 and CYP3A in the metabolism of ethanol and the metabolic activation and hepatotoxicity of paracetamol in animals [87–89, 99, 100, 168, 172]. In man, CYP1A2 does not seem to be quantitatively important in the metabolism of paracetamol to a toxic intermediate [173]. Because of dose dependence and species differences in the expression, activity and inducibility of these isoenzymes, it is not justifiable to extrapolate the results of animal studies to clinical conditions in man. At the end of the day, it does not matter too much which isoenzymes are responsible for the metabolism of paracetamol and ethanol in man because the toxic metabolic activation of paracetamol is not increased in chronic alcoholics. Although different isoenzymes of cytochrome P450 may be involved at different concentrations of paracetamol, it seems that the forms which are induced by ethanol are not primarily responsible for the toxic metabolic activation of paracetamol in man.

Conclusions

The interactions between paracetamol and ethanol are complex and many questions remain to be answered. In animals, chronic administration of ethanol causes microsomal enzyme induction with increased toxic metabolic activation of paracetamol and enhanced hepatotoxicity. Conversely, the acute administration of ethanol inhibits the potentially toxic oxidative metabolism of paracetamol and protects against liver damage. This protective effect disappears when the ethanol is eliminated and the time interval between the intake of ethanol and paracetamol is critical. The interactions between paracetamol and ethanol do not seem to be specific for any one isoform of cytochrome P450.

If the same circumstances apply in man as in animals, alcohol could increase or decrease the toxicity of paracetamol, or have no effect, depending on the timing and duration of alcohol consumption. Alcohol taken with paracetamol is likely to protect against liver toxicity and chronic alcoholics should be at their most vulnerable during the first few days of withdrawal. Clinical reports are difficult to interpret because insufficient attention has been given to the timing of alcohol intake in relation to the ingestion of paracetamol.

In contrast to the findings in animals, chronic alcoholics do not produce abnormally increased amounts of the potentially toxic metabolite of paracetamol. There is only modest, short-lived induction of CYP2E1 in chronic alcoholics and it seems that other isoenzymes are primarily responsible for the metabolic activation of paracetamol in man. In keeping with the metabolic data, there is no convincing clinical evidence to support the claims that chronic alcoholics are at increased risk of liver damage either following overdosage of paracetamol or with its therapeutic use. Such evidence as exists is purely anecdotal and similar toxicity has been reported in both circumstances in patients who are not alcoholic. Many of the patients who allegedly took paracetamol with 'therapeutic intent' had clearly taken major overdoses. Maximum therapeutic doses of paracetamol had no adverse effect on liver function in chronic alcoholics in their most susceptible state during withdrawal.

In many of the clinical reports cited, scientific discipline and the basic principles of pharmacoepidemiology have been disregarded and unsupportable conclusions have been drawn. By the same token, the authors of authoritative-sounding reviews and editorials on the subject of paracetamol and alcohol should recognize that they have a responsibility to impart the truth to their readers rather than to feed them a continuous diet of misinformation. Although the possibility that chronic alcoholics are at increased risk of paracetamol hepatotoxicity can by no means be excluded, the available evidence does not support claims for a major toxic interaction between ethanol and paracetamol in man. Further studies are required but until these issues are resolved, all patients who take alcohol in excess must continue to be considered at high risk following an overdose of paracetamol and be treated with *N*-acetylcysteine accordingly.

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